Position statement on the use of biosimilars in inflammatory bowel disease

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Position statement on the use of biosimilars in inflammatory bowel disease

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Summary

Biologics are effective and have a good safety profile in the treatment of inflammatory bowel disease. Biosimilars have recently become available as treatment option. They are biological agents that are highly similar to the original biologic compound in their structure, biological activity, efficacy and safety. This position paper summarises current knowledge on biosimilars and presents its statements on regulatory issues and clinical situation in order to provide clinicians adequate information for them to reach informed and appropriate shared decision-making with their patients.

Keywords: *inflammatory bowel disease, biologics, biosimilars*

Introduction

Since the introduction of infliximab in 1999, biologics have revolutionised medical treatment in inflammatory bowel disease (IBD), demonstrating high efficacy and a good safety profile [1, 2]. Today, physicians may choose from a variety of compounds to tailor their treatment to the individual patient. A biosimilar is a biological medicine highly similar to another, already approved biological medicine (called "reference product") in terms of structure, biological activity and efficacy, safety and immunogenicity profile. In Europe, the first biosimilar, a recombinant human growth hormone, was authorised in 2006 and as of today, over 40 biosimilars have entered the market. CT-P13 (manufactured by Celltrion, South Korea) was the first infliximab biosimilar to be approved by Swissmedic, the Swiss Regulatory Agency for Therapeutic Products [3]. By then, CT-P13 had already been approved by the European Medicines Agency (EMA) and later also received approval by the US Food and Drug Administration (FDA). Patents for many other biologics will expire in the near future and development of several biosimilars is underway. Therefore, physicians should be aware of the definition, approval process as well as the biochemical and clinical parameters that distinguish biosimilars from the reference product. Balanced information on biosimilars is paramount in making appropriate decisions for their patients.

This position statement by the Inflammatory Bowel Disease Net (IBDnet), an official working group of the Swiss Society of Gastroenterology, discusses several key aspects in the approval process and the clinical use of biosimilars. Using a Delphi-like technique, a panel of eight IBDnet delegates anonymously answered a total of 16 questions. All questions were rated using a Likert scale from 1 (strongly disagree) to 4 (strongly agree). Sufficient consensus was reached when the overall rating was 3 or higher, and the statement was accepted. In a final session, all statements were finalised on 18 June 2018 in Bern, Switzerland.

Regulatory process

– *To grant a licence for a biosimilar, Swissmedic requires biosimilarity, which means sufficient similarity of molecular structure, biological activity, efficacy, safety and immunogenicity.*

Swissmedic is the regulatory agency for all medicinal products and grants official authorisation before medicines can enter the market. Current Swissmedic guidance documentation on biosimilars requires that an applicant product is sufficiently similar with respect to structure, biological activity, efficacy, safety and immunogenicity in order to rule out relevant clinical differences with sufficient reliability [4]. This is similar to the requirements of the FDA, which allow "no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency" and the clarification by the EMA that a biosimilar must demonstrate similarity to the reference product in terms of quality characteristics, bio-

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logical activity, safety and efficacy based on a comprehensive comparability exercise [5, 6].

Unlike the approval of novel biologics, the approval pathway for biosimilars places more emphasis on comparative analytical data than on clinical studies. Biologics are very large molecules produced by living cells, so biosimilars are unlike small-molecule generics. Biosimilars, produced by a different cell clone with a reconstituted DNA template under different growth conditions, will never be identical to the reference product. Differences may arise from various steps within the manufacturing process and result in heterogeneity of the complex molecular structure [7, 8]. Thus, biosimilars are not generic equivalents of the reference product and require additional characterisation [4–6]. The molecular structure has to be analysed to ensure equivalent composition, especially since posttranslational modifications may differ in the various cell lines used for biosimilar production. This was the case for infliximab, which showed posttranslational changes to the Fc receptor, and only after additional *in vitro* studies was the manufacturer able to demonstrate that these differences were not of clinical significance [9, 10]. The observed differences from the originator have caused concern among physicians about the efficacy and safety of biosimilars [11, 12].

Although every biosimilar applicant has to demonstrate sufficient similarity in structure, biological activity, efficacy, safety and immunogenicity in order to receive regulatory approval, clinical efficacy has only to be proven in one indication of the reference product. In the case of CT-P13, Celltrion submitted one comparative clinical study in patients with rheumatoid arthritis and one supportive study in patients with ankylosing spondylitis that confirmed similar efficacy [13, 14]. Based on comparative studies, regulatory agencies will then decide if additional confirmatory clinical trials are warranted or if extrapolation of indications is enough to guarantee approval for each indication of the reference product.

In IBD, no specific trials have been conducted with biosimilars prior to approval. So far, the body of evidence suggests that the first infliximab biosimilar CT-P13 has similar efficacy and safety profiles to the reference infliximab [15–44], but some studies have been criticised [45] and strict pharmacovigilance is still warranted in the postmarketing setting.

Extrapolation of indications

– *Extrapolation of indications includes detailed biochemical and physicochemical evaluation of the biosimilar compound, clinical data on pharmacokinetic and pharmacodynamic equivalence to the reference product and clinical efficacy in one relevant sensitive patient population.*

Extrapolation is the regulatory and scientific process of applying clinical efficacy and safety data of the biosimilar derived from comparative studies in one therapeutic indication to all indications of the reference product. This is a key concept in the approval process of biosimilars. However, regulatory agencies base their decision to allow extrapolation of indications not only on clinical data, but also on the totality of evidence, which also includes data on the structural and physicochemical evaluation of the compound, as well as data on pharmacokinetic and pharmacodynamic equivalence to the reference product. Swissmedic states that an extrapolation of indications and dosage recommendations from the reference product to the biosimilar is possible only if it is scientifically justified and the associated risk to patient safety is acceptable [4]. The comparability between the biosimilar and the reference product, and thus the extrapolation to further indications and dosage recommendations, must be demonstrated in at least one sensitive indication and dosage or, if required, separately for each of the indications and dosage recommendations applied for.

To define the target population with the most sensitive disease may pose some difficulties. In order to demonstrate clinical equivalence, the therapeutic indication for the reference with the smallest difference from placebo should be selected, maximising the sensitivity to treatment effects. For the clinical trials of CT-P13, ankylosing spondylitis and rheumatoid arthritis were selected. First, in a phase I randomised double-blind study, equivalent pharmacokinetics, and tolerability, safety and efficacy of CT-P13 comparable to the reference infliximab in patients with ankylosing spondylitis were demonstrated [14]. Then, in a phase III randomised double-blind study, clinical efficacy was tested in patients with rheumatoid arthritis [13]. Again, this study showed comparable results for CT-P13 and the reference infliximab. However, because concomitant methotrexate was used in the PLANETRA, study patients with the “most sensitive indication” for comparison might not have selected.

Patients with IBD represent a very different patient population. In the randomised double-blind parallel-group NORSWITCH study, which tested interchangeability from the original infliximab to the biosimilar CT-P13, no significant difference in efficacy and safety was detected in the study population overall [22]. However, less than half of the study population consisted of patients with IBD (Crohn’s disease 32% and ulcerative colitis 19%). Although the study was not powered for subgroup analysis, patients with Crohn’s disease just barely fulfilled the noninferiority margin of 15%. In all other patient groups, the differences were much smaller. CT-P13 has decreased affinity for FcγRIII receptors and it is biologically plausible that this is linked to a decreased efficacy of CT-P13 in Crohn’s disease [45]. Usually, in order to demonstrate similar efficacy of a new compound compared with the reference product, noninferiority trials allow only 10% difference in the defined endpoints. This has raised some concern on the principle of extrapolation of indication for this class of biologics. Accordingly, Health Canada initially argued that differences in antibody-dependent cellular cytotoxicity (ADCC), afucosylation, and FcγRIIIa receptor binding were different for CT-P13. Full approval for the entire range of indications was subsequently granted only after additional data on physicochemical and biological properties, mechanism of action and clinical experience with the reference product were provided [46, 47].

There is consensus that extrapolation of indication needs convincing scientific justification and Swissmedic has issued guidance on the requirements that need to be fulfilled [4]. The concept of extrapolation will avoid unnecessary repetitions of studies and will save time and resources in

the regulatory process. Biosimilars are approved on a case-by-case and agency-by-agency basis after evaluating the totality of evidence from the entire development program.

Approved and future biosimilars for IBD in Switzerland

Currently, the infliximab biosimilar CT-P13 is the only compound approved in Switzerland for the use in IBD. It is produced by Celltrion (South Korea) and is marketed as Inflectra® by Pfizer Europe and as Remsima® by iQone (Germany). More biosimilars in IBD have already been approved by the EMA and the FDA (table 1), but not in Switzerland. However, this is likely to change in the near future, as a wave of biosimilars has just started to roll in and within the next years, the greater part of current revenues of biotech companies will likely be subject to competition from biosimilars (table 2).

Prescription, interchangeability and substitution

Prescription

– *All biologics and biosimilars should be prescribed by brand name and not by international nonproprietary name.*

Biosimilars should be clearly distinguishable from the reference product, and competing biosimilars and should be easily identifiable for patients, doctors and pharmacists alike. The international nonproprietary name (INN) of a biosimilar is not different from the original product, such as infliximab, which might be problematic for the traceability, especially in post-marketing studies and monitoring programmes [48]. It is paramount for patient safety that

Table 1: Biosimilars approved by the EMA and/or FDA.

Brand name (molecule)	INN (with suffix)	Regulatory agencies	Manufacturer / marketing	Authorisation date
Inflectra® (CT-P13)	Infliximab Inflximab-dyyb	EMA FDA	Pfizer Europe MA EEIG Celltrion Inc	Sept 2013 April 2016
Remsima® (CT-P13)	Infliximab	EMA	Celltrion Healthcare Hungary Kft	Sept 2013
Flixabi® (SB-2)	Infliximab	EMA	Samsung Bioepis UK Ltd (SBUK)	May 2016
Renflexis® (SB-2)	Infliximab-abda	FDA	Samsung Bioepis Co Ltd.	May 2017
Ixifi® (GP1111)	Infliximab-qbtx	FDA	Pfizer Inc.	Dec 2017
Zessly® (PF-06438179)	Infliximab	EMA	Sandoz GmbH	May 2018
Hulio® (FKB327)	Adalimumab	EMA	Mylan S.A.S.	Sep 2018
Idacio® Kromeya® (MSB11022)	Adalimumab	EMA	Fresenius Kabi Deutschland	Apr 2019
Amgevita® Amjevita® (ABP 501)	Adalimumab Adalimumab-atto	EMA FDA	Amgen Europe b.V. Amgen Inc.	Mar 2017 Sept 2016
Hyrimoz® (GP2017)	Adalimumab Adalimumab-adaz	EMA FDA	Sandoz GmbH Novartis	Jul 2018 Oct 2018
Cyltezo® (BI 695501)	Adalimumab-adbm	FDA	Boehringer Ingelheim	Aug 2017
Imraldi® Hadlima® (SB-5)	Adalimumab Adalimumab-bwwd	EMA FDA	Samsung Bioepis NL B.V. Samsung Bioepis Co Ltd.	Aug 2017 Mar 2019

EMA = European Medicines Agency; FDA = US Food and Drugs Administration; INN = international nonproprietary name Exemptia (ZRC-3197) adalimumab biosimilar is licensed in India only

Table 2: Biosimilars under development for possible use in inflammatory bowel disease.

Molecule		Manufacturer	Current status
Infliximab	BOW015*	Epirus Biopharmaceuticals	Phase III study
	NI-071	Nichi-Iko Pharmaceuticals	Phase III study
	STI-002	MabTech / Sorrento Therapeutics	Preclinical
Adalimumab	CHS-1420	Coherus	Phase III study
	M923	Momenta/Baxalta	Phase III study
	LBAL	LG Life Sciences / Mochida Pharmaceuticals	Preclinical
	MYL-1401A	Mylan Inc.	Preclinical
	PF-06410293	Pfizer Inc.	Phase III study
	BCD-057	Biocad	Preclinical
	ONS-3010	Oncobiologics	Preclinical
Golimumab	BOW100	Epirus Biopharmaceuticals	Preclinical
Certolizumab	PF6688	Pfenex	Preclinical
	Xcimanze	Xbrane	Preclinical

* BOW015 infliximab biosimilar is licensed in India only

the nomenclature for biosimilars is unique, and product information and batch manufacturing data allow for stringent pharmacovigilance.

The World Health Organization (WHO) recommendation proposes the addition of a unique identification code to identify biosimilars marketed under the INN. This qualifier would consist of a random addition of four consonants to the INN to label the manufacturer of the compound [49]. Similarly, the FDA recommends using a suffix of four lowercase letters to be added to the INN, three of which are distinct to the manufacturer of a given biosimilar [50]. In Europe, biosimilars share the same INN with the reference product. However, the EMA has applied the use of brand names in conjunction with the INN to distinguish between different manufacturers and allow traceability [6]. Swissmedic requires the INN to comply with WHO standards [4]. Thus, the name of a biosimilar must be either a creative name or the INN linked to a company name in order to easily identify biosimilars or the reference product.

Naming conventions are currently not consistent worldwide and the identification of biosimilars will remain a challenge. Global harmonisation is more than desirable in this matter as it has a direct impact on pharmacovigilance data and also on monitoring programmes for interchangeability, substitution and in the future possibly reimbursement [51].

Interchangeability

– *Prescribing physicians can interchange Inflectra® and Remsima®. Interchanging current Remicade® therapy with Inflectra® or Remsima® requires close efficacy and safety monitoring.*

"Interchangeability" is the medical practice of changing one medicine for another. Interchangeability is not automatically granted after regulatory approval of a biosimilar, but is designated after an additional review process by the regulatory agencies. In Europe, this is regulated on a national level, not by the EMA [52]. In contrast, the FDA has the authority to designate a biosimilar interchangeable with its reference product [53]. In order to be interchangeable, guidance by the FDA states that a biological product must be biosimilar, to have the same expected clinical effects and safety profile in any given patient, and to carry the similar risk when switching or continuing with the originator product if given more than once. In Switzerland, similar to other European countries, authorisation by Swissmedic does not contain any statement regarding whether a biosimilar can be used interchangeably with the reference product. It is recommended, that such a decision be made exclusively by the prescriber, i.e., the attending physician [4].

Inflectra® and Remsima® are identical biological products (both CT-P13) which are manufactured under identical conditions by the same manufacturer in South Korea (Celltrion), but are marketed by two different companies in Switzerland (Pfizer, iQone). As they are bioidentical, rather than biosimilar, a prescribing physician may interchange between them. However, when interchanging current Remicade® therapy with Inflectra® or Remsima®, close monitoring of efficacy and safety is required. Also, it is important to consider that with more independently developed biosimilars entering the market, the issue of interchangeability not only with the reference product but also among biosimilars will become even more important, especially since head-to-head comparisons of different biosimilars are unlikely to be carried out. For example, comparison data from erythropoietin biosimilars showed differences in pharmacodynamic properties among them, resulting in different dosing requirements [54].

The regulatory framework and post-marketing pharmacovigilance by the manufacturers must be stringent and reassure prescribers that an approved biosimilar can be administered safely and is in fact interchangeable with the reference product.

Substitution

– *Dispensing pharmacists are strongly encouraged not to substitute Remicade®, Inflectra® and Remsima®.*

Substitution describes the nationally regulated practice of dispensing one medical product instead of another interchangeable product at the pharmacy. This policy has been adopted in Switzerland for generic medication: pharmacists can substitute the original product at their discretion. Only if the physician has specifically prescribed an original product, must pharmacists inform the prescriber about the dispensed product in the event of substitution. For biologics, recommendations by Swissmedic advocate against automatic substitution by leaving the decision to interchange biological products exclusively with the prescribing physician [4]. Remicade® and Inflectra®/Remsima® cannot be substituted by the dispensing pharmacist without consent of prescribing clinician. There is general concern that automatic substitution might lead to dispensing mistakes that might potentially harm patients, especially when interchangeability has not directly been demonstrated in many specific clinical settings of a given disease. Also, there is doubt about pharmacovigilance, as pharmacists are not obliged to track batches (in contrast to physicians). It is known from the originator that batch-to-batch variations exist, and this will also be the case for any biosimilar [55]. Each biosimilar product should be easily distinguishable from the reference product and other biosimilars to ensure appropriate use, traceability and accurate reporting of adverse drug reactions. Otherwise a true signal on a biosimilar may be adjudicated to the safety database of the reference product, for example when the INN is used, and thereby go undetected in the system. Only the exchange of bioidenticals such as Inflectra® and Remsima® is considered unproblematic as they originate from the same biological material and manufacturing process.

Efficacy

– *Elective non-medical switch from Remicade® to CT-P13 does not impact efficacy. Head-to-head trials demonstrated comparable efficacy of Remicade® and CT-P13.*

Since the approval of CT-P13, reassuring data on its efficacy compared with the reference product has been reported in both non-IBD [56, 57] and IBD patients [15–43]. In IBD, real life data have emerged mainly from prospective open-label studies in stable patients on maintenance therapy who were switched to CT-P13, but also from obser-

vational studies in patients during induction therapy and from randomised controlled trials [22, 37, 43]. So far, these studies did not observe significant differences between the biosimilar and the reference product, demonstrating similar efficacy and safety for CT-P13. None of these studies reported differences in safety outcomes. Medium- and long-term data from several cohorts have also emerged and showed comparable effects in terms of efficacy, safety and immunogenicity.

In the PROSIT-BIO multicentre observational cohort, patients who were either naïve to biologics, or had been previously exposed to or had been switched from original infliximab were included [21]. Efficacy estimates on 434 patients who received a defined minimum of treatments were not different for naïve (74%), pre-exposed (62%) and switch patients (79%) after 24 weeks. In an extension study of the same cohort, the primary nonresponse rate was 6.4%, and 25.6% lost response during follow-up [33]. Among those who had responded to infliximab induction therapy, treatment persistence was similar in the three patient groups. Also, in another single-centre prospective observational study, no difference in terms of clinical remission (58 vs 47%), clinical response (13 vs 11%) or secondary loss of response (25 vs 42%) was detected in patients who switched to CT-P13 (n = 191) compared with those who continued on Remicade® (n = 19) during 12 months follow-up [28]. Data for patients with fistulising Crohn's disease are scarce.

A Korean post-marketing study in 173 patients that also included 12 patients with fistulising Crohn's disease showed clinical remission in 50% and clinical response in 67% after 30 weeks of treatment with CT-P13 [16]. No difference was seen between naïve patients and those who were switched to CT-P13.

A meta-analysis including 11 observational studies calculated that the pooled clinical response rates for Crohn's disease and ulcerative colitis after induction therapy with CT-P13 were 79% (95% confidence interval 65–88%) and 74% (65–82%), respectively, and during maintenance therapy (24–30 weeks) were 77% (67–86%) and 77% (67–85%), respectively [58]. This was comparable to the published response rate for the originator Remicade®. Sustained clinical response in patients who were switched from Remicade® to CTP-13 after 48–63 weeks was reported to be 75% (44–92%) for Crohn's disease and 83% (19–99%) for ulcerative colitis. Again, this was comparable to the expected annual loss of response rates of approximately 10–20% for Remicade® [59, 60].

Long-term data on patients who were switched to CT-P13 are limited. A prospective open-label nationwide cohort including 354 patients (209 with Crohn's disease) on CT-P13 found no difference in clinical efficacy after 54 weeks. Specifically, clinical remission and clinical response rates for Crohn's disease and ulcerative colitis were 65%/81% and 50%/66%, respectively [26]. Response rates in infliximab-naïve patients (54%/73% and 47%/51%, respectively) were significantly higher than in those with prior exposure to anti-tumour necrosis factor (TNF) agents (32%/44% and 27%/42%, respectively).Concomitant use of azathioprine did not affect clinical efficacy.

Another prospective observational open-label multicentre study from Sweden reported on 313 patients (195 with Crohn's disease) who were switched from Remicade® maintenance therapy to CT-P13 (Remsima®) and clinically assessed after 2, 6 and 12 months [29]. No significant changes in clinical activity, relevant biomarkers (faecal calprotectin, C-reactive protein) and serum concentration of infliximab (trough levels) were detected. Fourteen percent of patients with Crohn's disease and 13.8% with ulcerative colitis reported disease worsening as defined by the previously published NOR-SWITCH study [22]. Interestingly, 21.2% (7/33) with Crohn's disease and 23.8% (5/21) with ulcerative colitis who had clinically active disease at baseline were in clinical remission at 12 months. Similar results on infliximab trough levels after switching have recently been published from the SECURE study group [36]. After 16 weeks of CT-P13 treatment, infliximab serum concentrations were not inferior to baseline levels, and no significant changes in clinical and biochemical variables were noted.

The best long-term data come from a Norwegian single-centre cohort of 143 patients (99 Crohn's disease) who were switched to CT-P13 regardless of disease activity and concomitant treatment, and followed up prospectively for 18 months [30]. Altogether, 130 (91%) remained on biosimilar therapy and there was no change in disease activity scores or biomarkers.

Most recently, data from a large, real-world cohort from France including 5050 infliximab-naïve patients with Crohn's disease who received either Remicade® (n = 2551) or CT-P13 (n = 2499) have been published [41]. The composite end-point (death, Crohn's disease-related surgery, all-cause hospitalisation, and switch to another biologic therapy) was reached by 43.1% of Remicade® and 41.6% of CT-P13 recipients after 1 year. Rates of serious infection, tuberculosis and solid or haematological cancers did not differ between groups.

The first randomised data in IBD came from NOR-SWITCH trial (see above), which investigated patients with various immune-mediated inflammatory diseases who were switched from Remicade® to CT-P13 and followed up for 52 weeks [22]. For IBD, the primary endpoint of disease worsening was defined using the Harvey-Bradshaw Index (4-point change from baseline; score of 7 or greater) for Crohn's disease and the partial Mayo Score (3-point change from baseline; score of 5 or greater) for ulcerative colitis. Although the primary endpoint of the study fell within the predefined noninferiority margin of 15%, in the (underpowered) subgroup of IBD patients, disease worsening after switching to CT-P13 was almost significantly inferior to the reference product in patients with Crohn's disease. The adjusted difference in efficacy after switching to the biosimilar was 14.3% (95% CI 12.7–3.9%), which was considered too large by many as a clinically meaningful improvement of 12% has been described in support of patients with immune modulator therapy [35]. Recently, results from the open-label NOR-SWITCH EXTENSION trial have been published [42]. Patients who were switched to CT-P13 after 52 weeks were compared with patients who received CT-P13 over the 78-week study period. In Crohn's, disease worsening occurred in 20.6% (13 of 63 patients) in the maintenance group and in 13.1% (8 of 61) in the switch group; in ulcerative colitis, worsening occurred in 15.4% (6 of 39) and

2.9% (1 of 35) of patients in the maintenance and switch groups, respectively.

Results of the SIMILAR trial, a 12-week double-blind randomised controlled noninferiority trial investigating the efficacy of CT-P13 in patients with Crohn's disease and ulcerative colitis in remission who were switched from Remicade® are not published in full yet [61]. Preliminary results showed that switching was feasible and safe [37].

The first head-to-head trial in IBD was a multicentre double-blind randomised controlled phase III trial that aimed to demonstrate noninferiority in efficacy and to assess safety of CT-P13 against Remicade® in anti-TNF-naïve patients with active Crohn's disease [44]. In a four-arm design, 220 patients randomly received either CT-P13 or Remicade® until week 30 and then either remained on the same biological compound or switched to the other, and were followed-up until week 54. The primary outcome was the clinical response rate, defined as decrease in CDAI (Crohn's Disease Activity Index) score of >70 points at week 6. Secondary outcome measures included clinical response at week 30 and week 54, and clinical remission (CDAI <150) at the same time points. Clinical response rate was similar for CT-P13 and Remicade® at week 6 (69 vs 74%), week 30 (77 vs 75%) and week 54 (79 vs 76%). Similar results were seen for switch patients who received either CT-P13 (76%) or Remicade® (71%) at week 30. One-year safety including adverse drug reactions, serious adverse events and infections were similar among all treatment groups. Also, there was no clinically meaningful difference in immunogenicity.

So far, the results of the available randomised trial are in accordance with observational post-marketing studies that reported positive outcomes for efficacy in both Crohn's disease and ulcerative colitis.

Safety considerations

Adverse events

– *Frequency of adverse events is not different between patients maintained on Remicade® as compared with patients switched to CT-P13.*

The clinical safety of all biologics, including biosimilars, must be closely monitored during the post-marketing phase to detect less common safety signals. The approval process of biosimilars entails limited clinical exposure and certainly less clinical experience than with the reference product. Accurate data on adverse events associated with specific treatments should be provided to treating physicians to ensure that the prescription of any medication is safe and effective. In Switzerland, similar pharmacovigilance requirements apply for biosimilars and for a new active substance [4]. All identified and potential risks of the reference product and the biosimilar must be taken into consideration and a comprehensive plan for the continuing monitoring of safety following marketing approval must be submitted to Swissmedic. It is suggested that any pharmacovigilance plan should also include registries of adverse drug reactions that might be entered in major databases. IBDnet has developed a nationwide independent database to monitor biologics in IBD, including original and biosimilar products.

However, it is important to note that in Europe there are currently no standard requirements for post-approval safety monitoring programmes. These programmes are developed on a national level through discussion between the regulatory agency and the manufacturer, and already have to be included in the initial application for regulatory approval [62–64]. A serious limitation of pharmacovigilance is the underreporting of adverse events by healthcare providers [65, 66].It has been suggested that even in countries with high reporting rates less than 10% of all adverse drug reactions are reported. Successful pharmacovigilance depends primarily on reliable reporting by treating physicians.

So far, no unexpected safety issues have appeared after several years of biosimilar use. The frequency of adverse events for patients on CT-P13 is similar to that of patients treated with the reference product. Currently, more than 50 studies have evaluated the efficacy, safety and immunogenicity consequences of switching between different biosimilars over a range of indications in rheumatology, dermatology and gastroenterology, and showed no relevant difference in adverse events [25]. In a recent review including 11, mostly open-label, studies with 1007 IBD patients (507 with Crohn's disease) on the use of CT-P13, 9.2% of patients reported adverse side effects [67]. No difference in terms of safety was observed compared with the reference product effect (4.1% infusion-related reactions and 4.3% infections), which was comparable to data from the reference product (8.2%) and in line with results from the extension studies of PLANETAS and PLANETRA [56, 57]. Upcoming data from ongoing trials, such as SIMILAR [68], Connect-IBD [69] and SECURE [70], will shed more light on this topic. However, it has to be considered that even the growing body of evidence might still be insufficient to detect rare, unexpected adverse events. Ongoing pharmacovigilance and long-term follow-up of patients in large databases is warranted.

Immunogenicity

– *Immunogenicity is not different between patients treated with Remicade® and CT-P13. Immunogenicity is not different between patients maintained on Remicade® as compared with patients switched to CT-P13.*

Biologics are inherently immunogenic and may elicit antidrug antibodies in susceptible patients. This remains a major safety issue that cannot be predicted in preclinical studies. The presence of antidrug antibodies is associated with accelerated drug clearance, more common loss of response and higher risk of hypersensitivity reactions [71–73]. A recent systematic review analysed 68 studies including 14,651 patients with rheumatoid arthritis, ankylosing spondylarthritis and inflammatory bowel disease treated with TNF inhibitors, and found the cumulative incidence of antidrug antibodies to be 12.7% (infliximab 25.3%, adalimumab 6.9%, certolizumab pegol 3.8%, golimumab 1.2%) [74]. The incidence rate in IBD patients was similar (15.8%) and in all patients concomitant immunosuppressive therapy reduced the risk for antidrug antibodies. Overall, the presence of antidrug antibodies led to a 67% reduction of clinical response. Similar results have been reported in patients with IBD [75].

So far, the use of biosimilars shows similar efficacy and safety in different patient populations, but long-term data especially are still missing. To ensure equivalent immunogenicity between the biosimilar and the reference product is still a concern [76]. Immunogenicity data for the approval of CT-P13 were mainly based on *in vitro* studies and from clinical trials in rheumatology [13, 14]. Evidence from the randomised controlled PLANETRA trial showed a similar occurrence of antidrug antibodies after 1 year and, in the extension study, after 2 years [56]. However, patients in this study were all on immunosuppressive therapy with methotrexate, whereas IBD patients usually have combination therapy with azathioprine. This raises the question as to whether it is appropriate to extrapolate immunogenicity data across different patient populations.

Data on immunogenicity in patients switching from Remicade® to CT-P13 are limited [58]. In the NOR-SWITCH trial, no differences in antidrug antibodies were found overall [22] and among all the (underpowered) subgroups. The cross-immunogenicity of CT-P13 and Remicade® in IBD patients has elegantly been investigated in a series of *in vitro* studies [77]. Sera from 125 patients (69 positive for antidrug antibodies) and 14 healthy volunteers were tested. Cross-reactivity experiments were repeated after deglycosylation of Remicade®/CT-P13, IgG purification, excipient dialysis and monomer purification by size exclusion chromatography, and antidrug antibodies were tested for their functional inhibition of TNF-α binding to Remicade®/CT-P13 by competition assay. All sera containing anti-Remicade® antibodies were cross-reactive to Remsima® and titres were strongly correlated (Spearman's r 0.92–0.99 for all experiments). In a prospective, nationwide, multicentre, observational cohort with 353 consecutive IBD patients (209 Crohn's disease), biosimilar trough levels of patients pre-exposed to a TNF inhibitor were significantly lower at weeks 2, 14 and 30 in patients with Crohn's disease, but not ulcerative colitis, and were similar at week 6 and week 54 of follow-up [26]. The cumulative rate of antidrug antibodies was 33.8% for all IBD patients. A higher positivity rate at week 54 was seen only in patients with Crohn's disease (47 vs 26%; ulcerative colitis 47 vs 32%). Recently, the first long-term clinical data on immunogenicity in IBD after switching to CT-P13 became available. In a single centre prospective cohort study of 83 patients (57 Crohn's disease), no increase of antidrug antibodies was detected after >2 years follow-up [78]. These findings strongly suggest the presence of shared immune-dominant epitopes in CT-P13 and infliximab originator sequences.

Clinical situations

Bio-naïve patients

– *In bio-naïve patients considered for infliximab anti-TNF therapy, treatment can be initiated with Remicade®, Inflectra® or Remsima®.*

Most data on the use of infliximab biosimilars in IBD have been gathered from patients on maintenance therapy who were switched from the original product to CT-P13, and thus were considered exposed to an anti-TNF agent. As outlined above, a number of prospective observational studies, as well as randomised controlled trials have demonstrated similar clinical efficacy, safety and immunogenicity of CT-P13 compared with Remicade® in these patients [15–43]. The use of infliximab biosimilars in patients naïve to TNF inhibitors is less well investigated.

A meta-analysis that included 11 smaller studies showed response rates after induction and maintenance therapy for Crohn's disease (79 and 77%, respectively) and ulcerative colitis (74 and 77%, respectively), comparable to those published for Remicade® [58]. More recent data from observational cohorts have confirmed these initial results [20, 21, 26, 33, 41].

In patients with Crohn's disease, these results have also been confirmed by the first head-to-head trial in anti-TNF-naïve patients with active Crohn's disease [44]. Results on clinical response were similar up to week 54 with similar safety profiles and immunogenicity for Remicade® and CT-P13. It can therefore be considered safe to initiate infliximab therapy in bio-naïve patients with either Remicade®, Inflectra® or Remsima®. Caution should be used in patients with fistulising Crohn's disease, since only limited data on this patient subgroup are available [16].

Switch in class (for medical reasons)

– *Patients not responding adequately to Remicade® or losing response over time are not eligible for Inflectra® or Remsima®.*

– *Patients not responding adequately to Inflectra®/Remsima® or losing response over time are not eligible for Remicade®.*

– *Patients not responding adequately to adalimumab or certolizumab pegol or losing response over time are eligible for Remicade®, Inflectra® or Remsima®.*

Of all patients starting anti-TNF therapy, 10–30% may not respond to induction therapy (primary nonresponse), and an additional 23–46% of patients may lose response over time (secondary loss of response) or may become intolerant to TNF inhibitors [79]. There is no consensus on the definition of primary nonresponse, but insufficient clinical improvement during induction therapy is clinically accepted. However, the time-frame may vary depending on specific trial endpoints. Secondary loss of response is defined as clinical relapse (assessed using clinical symptom indices) during maintenance therapy after initial response to induction [80]. For patients who do not respond (enough) to biological therapy, dose intensification to regain therapeutic effect, combination therapy with an immunosuppressive drug, or a switch to another biological product may be considered. However, the latter option should only be chosen after a thorough work-up, as in general switching between different biologics can raise safety concerns and close monitoring of the patient is necessary. The work-up should first confirm active inflammation with objective methods, such as endoscopy, and infectious complications especially should be ruled out. Serum drug levels (trough levels) should then be measured and if not sufficient, antidrug antibodies should be sought to rule out immunity against the biological product.

Generally, low trough levels in the absence of antidrug antibodies can be managed by dose optimisation, whereas the presence of antidrug antibodies will require a switch to another biological. As antidrug antibodies are specific to a certain drug and do not cross-react, patients may be

switched within the therapeutic class to another anti-TNF agent and regain clinical response. However, patients who develop antidrug antibodies are more prone to immunogenicity when exposed to a different biological product. Biological products and their biosimilars share the same immune-dominant epitopes. Therefore, patients who develop antibodies to a reference drug with resultant loss of clinical response should not be switched to its biosimilar. Similarly, switching to a biosimilar is not a way to circumvent immunogenicity of originator [26]. If no antidrug antibodies are present and the serum drug concentration is adequate, clinical response to dose intensification is unlikely and patients should be switched to a biological product from another class.

Switch out of class (for medical reasons)

– *Patients not responding adequately or losing response over time to a biologic other than an anti-TNF agent are eligible for all anti-TNF biologics or biosimilars.*

For many years, TNF inhibitors were the only available biologics for treating patients with IBD. Vedolizumab and ustekinumab are two biological agents that have been introduced into the market only recently. Vedolizumab is a humanised monoclonal gut-selective antibody against α4β7 integrin and prevents migration of inflammatory cells into the inflamed mucosa. Ustekinumab is a monoclonal IgG1 antibody against the p40 subunit of interleukin-12 (IL-12) and interleukin-23 (IL-23) that targets both the T-helper 1 and T-helper 17 pathways involved in the pathogenesis of Crohn's disease. These drugs show a clinical benefit and seem to have a favourable safety profile [81, 82]. However, like anti-TNF agents, a significant number of patients do not respond to these drugs. Immunogenicity appears less important as the development of antidrug antibodies is very low for both vedolizumab (<5%) and ustekinumab (2.3%) [83, 84]. After careful clinical work-up, patients who do not respond adequately to biological therapy other than TNF inhibitors may be switched to either Remicade® or CT-P13. Currently, no data on clinical efficacy of TNF inhibitors as second-line therapy in patients pre-exposed to vedolizumab or ustekinumab are available.

Non-medical switch

– *Third party payer, administrator, and regulator driven switches from ongoing Remicade® therapy to CT-P13 are not recommended without prior approval of the prescribing physician.*

As outlined above, switching patients from Remicade® to CT-P13 is regarded as clinically effective and safe on the basis of several prospective open-label studies and randomised clinical trials [15–39, 43]. The annual healthcare costs for IBD patients have risen by 7 to 10% within the last 10 years, largely owing to treatment expenditures driven by increased use of biological agents [85]. With a steadily growing market, an increasing number of patients will receive biosimilars, and safety data will have to be continuously monitored. Overall, the biosimilars market has increased its value worldwide from around $2.5 billion in 2017 to $4.5 billion by the end of 2018 and is expected to expand to $61 billion by 2025 at an annual growth rate of 34% [86]. Given the large economic burden of biologic treatment of IBD, the main purpose of producing biosimilars is to reduce costs. In Central and Eastern Europe, the introduction of CT-P13 has resulted in a 20–60% price reduction for infliximab [87] and in Norway a 69% discount was offered for CT-P13 compared with Remicade® for its national supply in 2015 [88]. As more biosimilars enter the market, competition will further reduce prices, also for the original reference product. However, 56% of patients stated in a recent survey that safety and efficacy should be more important than lower cost of biosimilars [89]. In some countries, such Australia and Germany, automatic substitution is allowed for a select list of biosimilars, and in Germany patients have to pay the difference between the retail price and the reference reimbursement price, giving them an incentive to choose the cheaper (biosimilar) drug. Manufacturers are free to set a price for biosimilars in the US, Germany and the UK whereas other countries prohibit or limit manufacturer discounts [90]. In the US, insurance companies can increase biosimilar adoption rates by providing physicians with easy access to biosimilars (prior authorisation, precertification) while maintaining the administrative burden for the reference product [91]. In Switzerland, this policy has not been adopted. Healthcare providers in Switzerland are currently the only beneficiaries of switching a patient from a reference product to a less-expensive biosimilar. The risks inherent to drug switching are solely taken by the patient without having any financial benefits. Non-medical switch driven by third party payers, administrators and/or regulators in patients who have responded well to Remicade® should therefore be avoided.

Practical aspects – dosing, infusion management and monitoring

– *Handling and administration of Inflectra® and Remsima® are similar to those of Remicade®. Dose and administration interval of Remicade® should be maintained if a patient is switched to a biosimilar.*

– *Laboratory tests to detect anti-infliximab antibodies and infliximab trough levels are sensitive to Remicade®, Inflectra® and Remsima®*

The approval of biosimilars is based on clinical data that apply the same dose recommendations and route of administration as for the reference product. Once regulatory approval is granted, the same dose recommendations as for the original product can then be used for the biosimilar in all other indications. Also, storage and preparation, as well as infusion regimens, are identical for the reference product and corresponding biosimilar.

When switching from a biologic to the respective biosimilar, dose and treatment interval should be maintained. The available data show similar clinical efficacy after switching to a biosimilar without the need for dose adjustments [29]. Laboratory tests developed to measure infliximab trough levels and detect antidrug antibodies are equally sensitive for the reference product and any biosimilar. In a recent publication, 180 samples of 34 patients (16 patients with Crohn's disease) and 28 infliximab-naïve controls (12 patients with Crohn's disease) were analysed [92]. Seventy-six samples tested positive for antibodies to Rem-

icade®. Samples were then retested using a CT-P13 or a SB2 bridging assay and again all tested positive for infliximab antibodies resulting in 100% test agreement. Spearman's correlation was 0.98 for all comparisons, showing almost perfect alignment.

Patient perspectives

– *Many patients are not sufficiently informed about biosimilars, and thus are not familiar with the treatment. The decision to start biologic or biosimilar therapy should be taken in partnership with the patient.*

In Switzerland, as in many other countries, automatic substitution of biologics and biosimilars is discouraged by the regulatory authority, leaving the decision to interchange biological products with the prescribing physician. Any major treatment decision should always be taken in partnership with the patient, especially when highly potent biological medical products are introduced. The information presented to the patient should be transparent and comprehensive. Patients also have an obligation to engage in this discussion and participate actively in decision-making about their own therapy. However, a recent survey by the European Crohn's and Colitis Organization (ECCO) clearly demonstrated that patients are not familiar with many aspects of biological therapies including biosimilars [89]. Of 1181 participants, 62% had never heard of biosimilars and 40% of patients and 27% of patient associations felt they should be systematically informed. Their main concern was about safety (47%) and efficacy of treatment (40%), whereas only 31% had no concerns using biosimilars.

In order to make informed and appropriate treatment decisions with their patients, clinicians must understand the attributes and potential risks and benefits of biosimilars. In an anonymous survey among member of ECCO in 2013, 61% of participants felt little or no confidence in using biosimilars in their everyday clinical practice, regarded cost saving (89%) as the main advantage; extrapolation of indications and interchangeability of biosimilars were mentioned as main concerns [11]. In 2016, the survey was again sent out to ECCO members [12]. Interestingly, only a minority (19.5%) felt little or no confidence in the use of biosimilars, whereas cost saving (92.4%) was now mentioned as the main advantage and immunogenicity remained a main concern with biosimilars. Similar results were obtained in a survey among rheumatologists, dermatologists and gastroenterologists in the US, in which 84% of participants did not want to switch to biosimilars in stable patients and anticipated a negative impact on patient mental health (59%), treatment efficacy (57%), patient safety (53%) and physician office management (60%) [93].

Clearly, there is a need for education of patients and physicians alike. Effective communication needs to be addressed as shared decision making between healthcare professionals and patients will be a key aspect in order for biosimilars to be integrated effectively into clinical practice.

Discussion and next steps

In the near future we shall see an almost exponential growth of the biosimilar market with the introduction of a number of new products. After the introduction of CT-P13 in Switzerland, marketed as Inflectra® and Remsima®, IBD patients will soon be exposed to more infliximab biosimilars and also biosimilars of adalimumab and other biologics.

Biosimilars have several advantages: they reduce cost by competition with the original product; they offer enhanced accessibility to more affordable treatment options; and for companies they provide an incentive for innovative and patentable new biological product to maintain their market share in the future. However, biosimilars face a number of challenges. In order to gain wide acceptance, education of patients and healthcare providers should be the primary goal. Patients lack substantial knowledge on key aspects of biosimilars, which makes shared decision making difficult for doctors who are also still not completely comfortable with biosimilars. The concepts of extrapolation and interchangeability and uncertainties about patient safety are particular cause for concerns for many. More clinical data are needed to identify the ideal patient to receive or to be switched to a biosimilar. Also, switching between different biosimilars and multiple switching of originators and various biosimilars is a possible scenario for future patient care that is driven by fast development of new biosimilar molecules with likely reduction of treatment cost. However, this should be evaluated very carefully, as comparability between new biosimilars will not be tested at all. Therefore, regulatory legislation should be standardised and provide harmonised naming of biosimilars, clarify the directives on interchangeability of biological products and enable efficient pharmacovigilance. Long-term observational studies especially are recommended to improve the safety profile of biosimilars and increase confidence among patients and physicians.

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References

1 Baumgart DC, Sandborn WJ. Crohn's disease. Lancet. 2012;380(9853):1590–605. doi: http://dx.doi.org/10.1016/S0140-6736(12)60026-9. PubMed.
2 Danese S, Fiocchi C. Ulcerative colitis. N Engl J Med. 2011;365(18):1713–25. doi: http://dx.doi.org/10.1056/NEJMra1102942. PubMed.
3 Swiss Agency for Therapeutic Products. Swissmedic Journal. 2015;10. [cited 2019 February 16]; Available from: https://www.swissmedic.ch/dam/swissmedic/en/dokumente/stab/journal/swissmedic_journal102015.pdf.download.pdf/swissmedic_journal102015.pdf.
4 Swissmedic. Guidance Document Authorisation Biosimilar. 2018 [cited 2019 February 18]; Available from: https://www.swissmedic.ch/dam/swissmedic/en/dokumente/zulassung/zl/zl101_00_003d_wlverwaltungsverordnunganleitungzulassungaehnliche.pdf.download.pdf/ZL101_00_003e_WL%20Guidance%20document%20Authorisation%20Biosimilar.pdf.

5 US Food and Drug Administration. Biological Product Definitions. 2017 [cited 2019 February 18]; Available from: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM581282.pdf.

6 European Medicines Agency. Biosimilars in the EU. 2017 [cited 2019 February 18]; Available from: https://www.ema.europa.eu/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf.

7 Rathore N, Rajan RS. Current perspectives on stability of protein drug products during formulation, fill and finish operations. Biotechnol Prog. 2008;24(3):504–14. doi: http://dx.doi.org/10.1021/bp070462h. PubMed.

8 Lee JF, Litten JB, Grampp G. Comparability and biosimilarity: considerations for the healthcare provider. Curr Med Res Opin. 2012;28(6):1053–8. doi: http://dx.doi.org/10.1185/03007995.2012.686902. PubMed.

9 European Medicines Agency. Assessment Report: Inflectra. EMA/CHMP/589422/2013. 2013 [cited 2019 February 18]; Available from: https://www.ema.europa.eu/documents/assessment-report/inflectra-epar-public-assessment-report_en.pdf.

10 European Medicines Agency. Assessment Report: Remsima. EMEA/H/C/002576/0000. 2013 [cited 2019 February 18]; Available from: https://www.ema.europa.eu/documents/assessment-report/remsima-epar-public-assessment-report_en.pdf.

11 Danese S, Fiorino G, Michetti P. Viewpoint: knowledge and viewpoints on biosimilar monoclonal antibodies among members of the European Crohn's and Colitis Organization. J Crohn's Colitis. 2014;8(11):1548–50. doi: http://dx.doi.org/10.1016/j.crohns.2014.06.007. PubMed.

12 Danese S, Fiorino G, Michetti P. Changes in Biosimilar Knowledge among European Crohn's Colitis Organization [ECCO] Members: An Updated Survey. J Crohn's Colitis. 2016;10(11):1362–5. doi: http://dx.doi.org/10.1093/ecco-jcc/jjw090. PubMed.

13 Yoo DH, Hrycaj P, Miranda P, Ramiterre E, Piotrowski M, Shevchuk S, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis. 2013;72(10):1613–20. doi: http://dx.doi.org/10.1136/annrheumdis-2012-203090. PubMed.

14 Park W, Hrycaj P, Jeka S, Kovalenko V, Lysenko G, Miranda P, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis. 2013;72(10):1605–12. doi: http://dx.doi.org/10.1136/annrheumdis-2012-203091. PubMed.

15 Kang YS, Moon HH, Lee SE, Lim YJ, Kang HW. Clinical Experience of the Use of CT-P13, a Biosimilar to Infliximab in Patients with Inflammatory Bowel Disease: A Case Series. Dig Dis Sci. 2015;60(4):951–6. doi: http://dx.doi.org/10.1007/s10620-014-3392-z. PubMed.

16 Park SH, Kim YH, Lee JH, Kwon HJ, Lee SH, Park DI, et al. Post-marketing study of biosimilar infliximab (CT-P13) to evaluate its safety and efficacy in Korea. Expert Rev Gastroenterol Hepatol. 2015;9(sup1, Suppl 1):35–44. doi: http://dx.doi.org/10.1586/17474124.2015.1091309. PubMed.

17 Jung YS, Park DI, Kim YH, Lee JH, Seo PJ, Cheon JH, et al. Efficacy and safety of CT-P13, a biosimilar of infliximab, in patients with inflammatory bowel disease: A retrospective multicenter study. J Gastroenterol Hepatol. 2015;30(12):1705–12. doi: http://dx.doi.org/10.1111/jgh.12997. PubMed.

18 Farkas K, Rutka M, Bálint A, Nagy F, Bor R, Milassin Á, et al. Efficacy of the new infliximab biosimilar CT-P13 induction therapy in Crohn's disease and ulcerative colitis - experiences from a single center. Expert Opin Biol Ther. 2015;15(9):1257–62. doi: http://dx.doi.org/10.1517/14712598.2015.1064893. PubMed.

19 Smits LJ, Derikx LA, de Jong DJ, Boshuizen RS, van Esch AA, Drenth JP, et al. Clinical Outcomes Following a Switch from Remicade® to the Biosimilar CT-P13 in Inflammatory Bowel Disease Patients: A Prospective Observational Cohort Study. J Crohn's Colitis. 2016;10(11):1287–93. doi: http://dx.doi.org/10.1093/ecco-jcc/jjw087. PubMed.

20 Gecse KB, Lovász BD, Farkas K, Banai J, Bene L, Gasztonyi B, et al. Efficacy and Safety of the Biosimilar Infliximab CT-P13 Treatment in Inflammatory Bowel Diseases: A Prospective, Multicentre, Nationwide Cohort. J Crohn's Colitis. 2016;10(2):133–40. doi: http://dx.doi.org/10.1093/ecco-jcc/jjv220. PubMed.

21 Fiorino G, Manetti N, Armuzzi A, Orlando A, Variola A, Bonovas S, et al.; PROSIT-BIO Cohort. The PROSIT-BIO Cohort: A Prospective Observational Study of Patients with Inflammatory Bowel Disease Treated with Infliximab Biosimilar. Inflamm Bowel Dis. 2017;23(2):233–43. doi: http://dx.doi.org/10.1097/MIB.0000000000000995. PubMed.

22 Jørgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, Haavardsholm EA, et al.; NOR-SWITCH study group. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet. 2017;389(10086):2304–16. doi: http://dx.doi.org/10.1016/S0140-6736(17)30068-5. PubMed.

23 Buer LC, Moum BA, Cvancarova M, Warren DJ, Medhus AW, Høivik ML. Switching from Remicade® to Remsima® is well Tolerated and Feasible: A Prospective, Open-label Study. J Crohn's Colitis. 2017;11(3):297–304. PubMed.

24 Smits LJT, Grelack A, Derikx LAAP, de Jong DJ, van Esch AAJ, Boshuizen RS, et al. Long-Term Clinical Outcomes After Switching from Remicade® to Biosimilar CT-P13 in Inflammatory Bowel Disease. Dig Dis Sci. 2017;62(11):3117–22. doi: http://dx.doi.org/10.1007/s10620-017-4661-4. PubMed.

25 Moots R, Azevedo V, Coindreau JL, Dörner T, Mahgoub E, Mysler E, et al. Switching Between Reference Biologics and Biosimilars for the Treatment of Rheumatology, Gastroenterology, and Dermatology Inflammatory Conditions: Considerations for the Clinician. Curr Rheumatol Rep. 2017;19(6):37. doi: http://dx.doi.org/10.1007/s11926-017-0658-4. PubMed.

26 Gonczi L, Gecse KB, Vegh Z, Kurti Z, Rutka M, Farkas K, et al. Long-term Efficacy, Safety, and Immunogenicity of Biosimilar Infliximab After One Year in a Prospective Nationwide Cohort. Inflamm Bowel Dis. 2017;23(11):1908–15. doi: http://dx.doi.org/10.1097/MIB.0000000000001237. PubMed.

27 Guerra Veloz MF, Argüelles-Arias F, Castro Laria L, Maldonado Pérez B, Benítez Roldan A, Perea Amarillo R, et al. Loss of efficacy and safety of the switch from infliximab original to infliximab biosimilar (CT-P13) in patients with inflammatory bowel disease. World J Gastroenterol. 2018;24(46):5288–96. doi: http://dx.doi.org/10.3748/wjg.v24.i46.5288. PubMed.

28 Ratnakumaran R, To N, Gracie DJ, Selinger CP, O'Connor A, Clark T, et al. Efficacy and tolerability of initiating, or switching to, infliximab biosimilar CT-P13 in inflammatory bowel disease (IBD): a large single-centre experience. Scand J Gastroenterol. 2018;53(6):700–7. doi: http://dx.doi.org/10.1080/00365521.2018.1464203. PubMed.

29 Bergqvist V, Kadivar M, Molin D, Angelison L, Hammarlund P, Olin M, et al. Switching from originator infliximab to the biosimilar CT-P13 in 313 patients with inflammatory bowel disease. Therap Adv Gastroenterol. 2018;11:. doi: http://dx.doi.org/10.1177/1756284818801244. PubMed.

30 Høivik ML, Buer LCT, Cvancarova M, Warren DJ, Bolstad N, Moum BA, et al. Switching from originator to biosimilar infliximab - real world data of a prospective 18 months follow-up of a single-centre IBD population. Scand J Gastroenterol. 2018;53(6):692–9. doi: http://dx.doi.org/10.1080/00365521.2018.1463391. PubMed.

31 Keil R, Wasserbauer M, Zádorová Z, Hajer J, Drastich P, Wohl P, et al. Clinical monitoring: infliximab biosimilar CT-P13 in the treatment of Crohn's disease and ulcerative colitis. Scand J Gastroenterol. 2016;51(9):1062–8. doi: http://dx.doi.org/10.3109/00365521.2016.1149883. PubMed.

32 Tursi A, Allegretta L, Chiri S, Della Valle N, Elisei W, Forti G, et al. Effectiveness and safety of infliximab biosimilar CT-P13 in treating ulcerative colitis: a real-life experience in IBD primary centers. Minerva Gastroenterol Dietol. 2017;63(4):313–8. doi: http://dx.doi.org/10.23736/S1121-421X.17.02402-3. PubMed.

33 Armuzzi A, Fiorino G, Variola A, Manetti N, Fries W, Orlando A, et al.; PROSIT Investigators. The PROSIT Cohort of Infliximab Biosimilar in IBD: A Prolonged Follow-up on the Effectiveness and Safety Across Italy. Inflamm Bowel Dis. 2019;25(3):568–79. doi: http://dx.doi.org/10.1093/ibd/izy264. PubMed.

34 Schmitz EMH, Boekema PJ, Straathof JWA, van Renswouw DC, Brunsveld L, Scharnhorst V, et al. Switching from infliximab innovator to biosimilar in patients with inflammatory bowel disease: a 12-month multicentre observational prospective cohort study. Aliment Pharmacol Ther. 2018;47(3):356–63. doi: http://dx.doi.org/10.1111/apt.14453. PubMed.

35 Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al.; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010;362(15):1383–95. doi: http://dx.doi.org/10.1056/NEJMoa0904492. PubMed.

36 Strik AS, van de Vrie W, Bloemsaat-Minekus JPJ, Nurmohamed M, Bossuyt PJJ, Bodelier A, et al.; SECURE study group. Serum concentrations after switching from originator infliximab to the biosimilar CT-P13

in patients with quiescent inflammatory bowel disease (SECURE): an open-label, multicentre, phase 4 non-inferiority trial. Lancet Gastroenterol Hepatol. 2018;3(6):404–12. doi: http://dx.doi.org/10.1016/S2468-1253(18)30082-7. PubMed.

37 Volkers A, Jansen J. Similar Trial - Efficacy of Infliximab-Biosimilar compared to Infliximab-Biological in Patients with Inflammatory Bowel Disease - a Randomized, Controlled, Double-Blind, Phase 4, Noninferiority Trial. United European Gastroenterol J. 2017;5(A307):P0409. Available from: https://www.ueg.eu/education/document/similar-trial-efficacy-of-infliximab-biosimilar-compared-to-infliximab-biological-in-patients-with-inflammatory-bowel-disease-in-remission-a-randomized-co.

38 Hlavaty T, Krajčovičová A, Šturdík I, Letkovský J, Koller T, Tóth J, et al. Biosimilar infl iximab CT-P13 treatment in patients with infl am matory bowel diseases – a one-year, single-centre retrospective study. Gastroenterol Hepatol (N Y). 2016;70(1):27–36. doi: http://dx.doi.org/10.14735/amgh201627.

39 Jahnsen J, Detlie TE, Vatn S, Ricanek P. Biosimilar infliximab (CT-P13) in the treatment of inflammatory bowel disease: A Norwegian observational study. Expert Rev Gastroenterol Hepatol. 2015;9(sup1, Suppl 1):45–52. doi: http://dx.doi.org/10.1586/17474124.2015.1091308. PubMed.

40 Ilias A, Szanto K, Gonczi L, Kurti Z, Golovics PA, Farkas K, et al. Outcomes of Patients With Inflammatory Bowel Diseases Switched From Maintenance Therapy With a Biosimilar to Remicade. Clin Gastroenterol Hepatol. 2019. In production. doi: http://dx.doi.org/10.1016/j.cgh.2018.12.036. PubMed.

41 Meyer A, Rudant J, Drouin J, Weill A, Carbonnel F, Coste J. Effectiveness and Safety of Reference Infliximab and Biosimilar in Crohn Disease: A French Equivalence Study. Ann Intern Med. 2019;170(2):99–107. doi: http://dx.doi.org/10.7326/M18-1512. PubMed.

42 Goll GL, Jørgensen KK, Sexton J, Olsen IC, Bolstad N, Haavardsholm EA, et al. Long-term efficacy and safety of biosimilar infliximab (CT-P13) after switching from originator infliximab: open-label extension of the NOR-SWITCH trial. J Intern Med. 2019;285(6):653–69. doi: http://dx.doi.org/10.1111/joim.12880. PubMed.

43 Jorgensen KK, Goll GL, Sexton J, Olsen IC, Bolstad N, Lundin KE, et al. Long-term efficacy and safety of biosimilar infliximab (CT-P13) after switching from originator infliximab: Explorative subgroup analyses in IBD from the NOR-SWITCH EXTENSION trial. J Crohn's Colitis. 2018;12(supplement_1):348–9. doi: http://dx.doi.org/10.1093/ecco-jcc/jjx180.610.

44 Ye BD, Pesegova M, Alexeeva O, Osipenko M, Lahat A, Dorofeyev A, et al. Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease: an international, randomised, double-blind, phase 3 non-inferiority study. Lancet. 2019;393(10182):1699–707. doi: http://dx.doi.org/10.1016/S0140-6736(18)32196-2. PubMed.

45 Michetti P. Efficacy of infliximab biosimilars in patients with Crohn's disease. Lancet. 2017;390(10111):2435. doi: http://dx.doi.org/10.1016/S0140-6736(17)32459-5. PubMed.

46 Health Canada. Summary Basis of Decision Remsima. [cited 2019 February 18]; Available from: https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?linkID=SBD00330#paatDiv.

47 Health Canada. Summary Basis of Decision Inflectra. [cited 2019 February 18]; Available from: https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?lang=en&linkID=SBD00253.

48 Vermeer NS, Spierings I, Mantel-Teeuwisse AK, Straus SM, Giezen TJ, Leufkens HG, et al. Traceability of biologicals: present challenges in pharmacovigilance. Expert Opin Drug Saf. 2015;14(1):63–72. doi: http://dx.doi.org/10.1517/14740338.2015.972362. PubMed.

49 World Health Organization. Guidance on the use of International Nonproprietary Names (INNs) for pharmaceutical substances. 2017 [cited 2019 February 18]; Available from: https://www.who.int/medicines/services/inn/FINAL_WHO_PHARM_S_NOM_1570_web.pdf?ua=1.

50 US Food and Drug Administration. Nonproprietary Naming of Biological Products. Guidance for Industry. 2017 [cited 2019 February 18]; Available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm459987.pdf.

51 Grampp G, Felix T. Pharmacovigilance Considerations for Biosimilars in the USA. BioDrugs. 2015;29(5):309–21. doi: http://dx.doi.org/10.1007/s40259-015-0137-2. PubMed.

52 European Medicines Agency. European Medicines Agency procedural advice for users of the centralised procedure for similar biological medicinal products applications. 2019 [cited 2019 February 19]; Available from: https://www.ema.europa.eu/documents/regulatory-procedural-guideline/european-medicines-agency-procedural-advice-users-centralised-procedure-similar-biological-medicinal_en-0.pdf.

53 US Food and Drug Administration. Considerations in Demonstrating Interchangeability With a Reference Product. Guidance for Industry. Draft Guidance. 2017 [cited 2019 February 19]; Available from: http://academy.gmp-compliance.org/guidemgr/files/UCM537135.pdf.

54 Wizemann V, Rutkowski B, Baldamus C, Scigalla P, Koytchev R; Epoetin Zeta Study Group. Comparison of the therapeutic effects of epoetin zeta to epoetin alfa in the maintenance phase of renal anaemia treatment. Curr Med Res Opin. 2008;24(3):625–37. doi: http://dx.doi.org/10.1185/030079908X273264. PubMed.

55 Planinc A, Dejaegher B, Vander Heyden Y, Viaene J, Van Praet S, Rappez F, et al. Batch-to-batch N-glycosylation study of infliximab, trastuzumab and bevacizumab, and stability study of bevacizumab. Eur J Hosp Pharm Sci Pract. 2017;24(5):286–92. doi: http://dx.doi.org/10.1136/ejhpharm-2016-001022. PubMed.

56 Yoo DH, Prodanovic N, Jaworski J, Miranda P, Ramiterre E, Lanzon A, et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Ann Rheum Dis. 2017;76(2):355–63. doi: http://dx.doi.org/10.1136/annrheumdis-2015-208786. PubMed.

57 Park W, Yoo DH, Miranda P, Brzosko M, Wiland P, Gutierrez-Ureña S, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. Ann Rheum Dis. 2017;76(2):346–54. doi: http://dx.doi.org/10.1136/annrheumdis-2015-208783. PubMed.

58 Komaki Y, Yamada A, Komaki F, Micic D, Ido A, Sakuraba A. Systematic review with meta-analysis: the efficacy and safety of CT-P13, a biosimilar of anti-tumour necrosis factor-α agent (infliximab), in inflammatory bowel diseases. Aliment Pharmacol Ther. 2017;45(8):1043–57. doi: http://dx.doi.org/10.1111/apt.13990. PubMed.

59 Roda G, Jharap B, Neeraj N, Colombel JF. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. Clin Transl Gastroenterol. 2016;7(1):. doi: http://dx.doi.org/10.1038/ctg.2015.63. PubMed.

60 Qiu Y, Chen BL, Mao R, Zhang SH, He Y, Zeng ZR, et al. Systematic review with meta-analysis: loss of response and requirement of anti-TNF-α dose intensification in Crohn's disease. J Gastroenterol. 2017;52(5):535–54. doi: http://dx.doi.org/10.1007/s00535-017-1324-3. PubMed.

61 Efficacy and safety of infliximab-biosimilar (Inflectra) compared to infliximab-innovator (Remicade) in patients with inflammatory bowel disease in remission: the SIMILAR Trial. ClinicalTrials.gov [cited 2019 February y14]; Available from: https://clinicaltrials.gov/ct2/show/NCT02452151.

62 US Food and Drug Administration. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Guidance for Industry. Guidance for Industry. 2015 [cited 2019 February 16]; Available from: https://www.fda.gov/downloads/drugs/%20guidancecomplianceregulatoryinformation/guidances/ucm291128.pdf.

63 World Health Organization. Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs). WHO Expert Committee on Biological Standardization. 2016 [cited 2019 Feburar 18]; Available from: https://www.who.int/biologicals/biotherapeutics/WHO_TRS_1004_web_Annex_2.pdf?ua=1.

64 European Medicines Agency. Guideline on Similar Biological Medicinal Products. CHMP/437/04 Rev 1. 2014 [cited 2019 February 18]; Available from: https://www.ema.europa.eu/documents/scientific-guideline/guideline-similar-biological-medicinal-products-rev1_en.pdf.

65 Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Determinants of under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2009;32(1):19–31. doi: http://dx.doi.org/10.2165/00002018-200932010-00002. PubMed.

66 Hazell L, Shakir SA. Under-reporting of adverse drug reactions : a systematic review. Drug Saf. 2006;29(5):385–96. doi: http://dx.doi.org/10.2165/00002018-200629050-00003. PubMed.

67 Radin M, Sciascia S, Roccatello D, Cuadrado MJ. Infliximab Biosimilars in the Treatment of Inflammatory Bowel Diseases: A Systematic Review. BioDrugs. 2017;31(1):37–49. doi: http://dx.doi.org/10.1007/s40259-016-0206-1. PubMed.

68 Efficacy and Safety of Infliximab-biosimilar (Inflectra) Compared to Infliximab-innovator (Remicade) in Patients With Inflammatory Bowel Disease in Remission: the SIMILAR Trial (SIMILAR). [cited 2019 February 19]; Available from: https://clinicaltrials.gov/ct2/show/NCT02452151.

69 Post-Marketing Use Of CT-P13 (Infliximab) For Standard Of Care Treatment Of Inflammatory Bowel Disease (CONNECT-IBD). ClinicalTrials.gov, [cited 2019 February 19]; Available from: https://clinicaltrials.gov/ct2/show/NCT02539368.

70 An open-label, multicentre, phase IV study to investigate the infliximab serum concentration of Remsima™ (infliximab biosimilar) after switching from Remicade (infliximab) in subjects with Crohn's Disease (CD), Ulcerative Colitis (UC) or Rheumatoid Arthritis (RA) in stable remission. EU Clinical Trials Register, [cited 2019 February 19]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-004904-31/NL.

71 Baert F, Noman M, Vermeire S, Van Assche G, D' Haens G, Carbonez A, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med. 2003;348(7):601–8. doi: http://dx.doi.org/10.1056/NEJMoa020888. PubMed.

72 Nanda KS, Cheifetz AS, Moss AC. Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD): a meta-analysis. Am J Gastroenterol. 2013;108(1):40–7, quiz 48. doi: http://dx.doi.org/10.1038/ajg.2012.363. PubMed.

73 Vande Casteele N, Khanna R, Levesque BG, Stitt L, Zou GY, Singh S, et al. The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease. Gut. 2015;64(10):1539–45. doi: http://dx.doi.org/10.1136/gutjnl-2014-307883. PubMed.

74 Thomas SS, Borazan N, Barroso N, Duan L, Taroumian S, Kretzmann B, et al. Comparative Immunogenicity of TNF Inhibitors: Impact on Clinical Efficacy and Tolerability in the Management of Autoimmune Diseases. A Systematic Review and Meta-Analysis. BioDrugs. 2015;29(4):241–58. doi: http://dx.doi.org/10.1007/s40259-015-0134-5. PubMed.

75 Vermeire S, Gils A, Accossato P, Lula S, Marren A. Immunogenicity of biologics in inflammatory bowel disease. Therap Adv Gastroenterol. 2018;11:. doi: http://dx.doi.org/10.1177/1756283X17750355. PubMed.

76 Lee H. Is extrapolation of the safety and efficacy data in one indication to another appropriate for biosimilars? AAPS J. 2014;16(1):22–6. doi: . Correction in: AAPS J. 2015;17(6):1520–1. doi: http://dx.doi.org/10.1208/s12248-013-9534-y. PubMed.

77 Ben-Horin S, Yavzori M, Benhar I, Fudim E, Picard O, Ungar B, et al. Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima. Gut. 2016;65(7):1132–8. doi: http://dx.doi.org/10.1136/gutjnl-2015-309290. PubMed.

78 Smits LJT, van Esch AAJ, Derikx LAAP, Boshuizen R, de Jong DJ, Drenth JPH, et al. Drug Survival and Immunogenicity After Switching From Remicade to Biosimilar CT-P13 in Inflammatory Bowel Disease Patients: Two-year Follow-up of a Prospective Observational Cohort Study. Inflamm Bowel Dis. 2019;25(1):172–9. doi: http://dx.doi.org/10.1093/ibd/izy227. PubMed.

79 Papamichael K, Gils A, Rutgeerts P, Levesque BG, Vermeire S, Sandborn WJ, et al. Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD: evolution in the definition and management of primary nonresponse. Inflamm Bowel Dis. 2015;21(1):182–97. doi: http://dx.doi.org/10.1097/MIB.0000000000000202. PubMed.

80 Allez M, Karmiris K, Louis E, Van Assche G, Ben-Horin S, Klein A, et al. Report of the ECCO pathogenesis workshop on anti-TNF therapy failures in inflammatory bowel diseases: definitions, frequency and pharmacological aspects. J Crohn's Colitis. 2010;4(4):355–66. doi: http://dx.doi.org/10.1016/j.crohns.2010.04.004. PubMed.

81 Amiot A, Serrero M, Peyrin-Biroulet L, Filippi J, Pariente B, Roblin X, et al.; OBSERV-IBD study group and the GETAID. One-year effectiveness and safety of vedolizumab therapy for inflammatory bowel disease: a prospective multicentre cohort study. Aliment Pharmacol Ther. 2017;46(3):310–21. doi: http://dx.doi.org/10.1111/apt.14167. PubMed.

82 Ma C, Fedorak RN, Kaplan GG, Dieleman LA, Devlin SM, Stern N, et al. Long-term Maintenance of Clinical, Endoscopic, and Radiographic Response to Ustekinumab in Moderate-to-Severe Crohn's Disease: Real-world Experience from a Multicenter Cohort Study. Inflamm Bowel Dis. 2017;23(5):833–9. doi: http://dx.doi.org/10.1097/MIB.0000000000001074. PubMed.

83 Rosario M, Dirks NL, Gastonguay MR, Fasanmade AA, Wyant T, Parikh A, et al. Population pharmacokinetics-pharmacodynamics of vedolizumab in patients with ulcerative colitis and Crohn's disease. Aliment Pharmacol Ther. 2015;42(2):188–202. doi: http://dx.doi.org/10.1111/apt.13243. PubMed.

84 Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al.; UNITI–IM-UNITI Study Group. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2016;375(20):1946–60. doi: http://dx.doi.org/10.1056/NEJMoa1602773. PubMed.

85 Pillai N, Dusheiko M, Maillard MH, Rogler G, Brüngger B, Bähler C, et al.; Swiss IBD Cohort Study Group. The Evolution of Health Care Utilisation and Costs for Inflammatory Bowel Disease Over Ten Years. J Crohn's Colitis. 2019;13(6):744–54. doi: http://dx.doi.org/10.1093/ecco-jcc/jjz003. PubMed.

86 Grand View Research. Biosimilars Market Size, Share & Trends Analysis Report By Product, By Application (Oncology, Growth Hormone, Blood Disorders, Chronic & Autoimmune Disorders), By Region, And Segment Forecasts, 2018 - 2025. Jul 2018 [cited 2019 February 20]; Available from: https://www.grandviewresearch.com/industry-analysis/biosimilars-market.

87 Braun J, Kudrin A. Switching to biosimilar infliximab (CT-P13): Evidence of clinical safety, effectiveness and impact on public health. Biologicals. 2016;44(4):257–66. doi: http://dx.doi.org/10.1016/j.biologicals.2016.03.006. PubMed.

88 Generics and Biosimilars Initiative Journal Online. Huge discount on biosimilar infliximab in Norway. [cited 2019 February 19]; Available from: http://www.gabionline.net/Biosimilars/General/Huge-discount-on-biosimilar-infliximab-in-Norway.

89 Peyrin-Biroulet L, Lönnfors S, Roblin X, Danese S, Avedano L. Patient Perspectives on Biosimilars: A Survey by the European Federation of Crohn's and Ulcerative Colitis Associations. J Crohn's Colitis. 2017;11(1):128–33. doi: http://dx.doi.org/10.1093/ecco-jcc/jjw138. PubMed.

90 Canadian Agency for Drugs and Technologies in Health (CADTH). International Policies on the Appropriate Use of Biosimilar Drugs Enviromental Scan 2018 [cited 2019 February 19]; Available from: https://www.cadth.ca/sites/default/files/pdf/es0333_international-policies-on-use-of-biosimilar-drugs.pdf.

91 Manolis CH, Rajasenan K, Harwin W, McClelland S, Lopes M, Farnum C. Biosimilars: Opportunities to Promote Optimization Through Payer and Provider Collaboration. J Manag Care Spec Pharm. 2016;22(9, Suppl):S3–9. doi: http://dx.doi.org/10.18553/jmcp.2016.22.9-a.s3. PubMed.

92 Fiorino G, Ruiz-Argüello MB, Maguregui A, Nagore D, Correale C, Radice S, et al. Full Interchangeability in Regard to Immunogenicity Between the Infliximab Reference Biologic and Biosimilars CT-P13 and SB2 in Inflammatory Bowel Disease. Inflamm Bowel Dis. 2018;24(3):601–6. doi: http://dx.doi.org/10.1093/ibd/izx086. PubMed.

93 Teeple A, Ellis LA, Huff L, Reynolds C, Ginsburg S, Howard L, et al. Physician attitudes about non-medical switching to biosimilars: results from an online physician survey in the United States. Curr Med Res Opin. 2019;35(4):611–7. doi: http://dx.doi.org/10.1080/03007995.2019.1571296. PubMed.